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A CONTRIBUTION TO THE PATHOLOGICAL ANATOMY OF ROCKY MOUNTAIN SPOTTED FEVER.*†

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Six postmortem examinations were made by Dr. Ricketts on the bodies of persons dying of the disease. The cutaneous hemorrhages were general in all and varied from petechiae no more than pin-head sized to large confluent and grotesquely shaped, bluish-black hemorrhages covering all parts of the body except the palms and soles. In a few of the bodies hemorrhages were observed in the pleurae or omentum, in one instance in the substance of the lungs. The superficial and visceral lymph glands were moderately enlarged. An icterus was always present. Enlargement of the spleen is quite characteristic of the disease. It was from two to three times the normal size in all the bodies examined. In other respects it was but little altered, fairly firm, and moderately hyperemic. A large infarct was present in one instance. The large veins and right chamber of the heart were distended with blood. The liver and kidneys were enlarged and hyperemic and in both organs varying degrees of cloudy swelling, and fatty degeneration were met with. The changes in the other organs were neither marked nor constant enough to deserve mention, with the exception of the bone marrow. In two bodies where this was examined the marrow of the long bones was red to bluish red.

In monkeys and guinea-pigs the changes are like those in man with the exception of the absence of generalized cutaneous hemorrhages; in white-skinned guinea-pigs these are sometimes seen. Localized hemorrhages with necrosis of the scrotum, vulva, or prepuce are a more constant result of the disease in these animals;

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† Several years before the death of Dr. Ricketts he and I planned a joint work on Rocky Mountain spotted fever to which he was to contribute accounts of its etiology, clinical aspects, and gross morbid anatomy, and I a study of the minute changes. The plan dealt with a monographic consideration of the disease. Some of the phases of this work were to be reported by me at the last meeting of the Association of Pathologists and Bacteriologists in Washington, May, 1910, and for this purpose he sent me notes of the gross changes he had observed in human and animal bodies. No report was made, news of his death arriving during the meeting. His observations are included in the following account.

occasionally the ears become necrotic.[1] Hemorrhages are also met with in the lymph glands in guinea-pigs. In other respects the lesions of both guinea-pigs and monkeys are quite like those in man.

It will not be necessary except in a few instances to compare the microscopic changes in human tissues with those in animals; they may be considered as a whole. The animal tissues examined were from six monkeys and 32 guinea-pigs; the human tissues from the six bodies mentioned.

The changes are of two sorts, those connected with the occlusion of vessels and the more diffuse lesions affecting entire groups of organs. The diffuse changes are hyperplasia of lymphoid tissues and cloudy swelling and acute fatty changes in organs commonly the seat of such lesions in acute infectious diseases. The focal lesions are more varied in their nature since they include not only the processes leading up to the occlusion of vessels, but the results of such obstructions, necrosis in different degrees and the hemorrhages responsible for so many of the clinical and gross anatomic features of the disease as well as for the name "spotted fever." In sections of the skin, liver, kidney, spleen, and adrenal both vascular occlusion and the necroses resulting from obstruction were present. In the lung and heart the capillaries and small veins were found practically occluded with leukocytes, but there were no serious consequences of these conditions with exception of minute hemorrhages beneath the endocardium.

In the least marked lesions of this sort the vessels contain simply an excess of small and large lymphocytes and some of the latter cells have as inclusions red cells or other leukocytes. In the more obvious occlusions agglutinated red cells, fibrin, and polymorphonuclear leukocytes are also present. The agglutinated red cells are often stained a deeper red with eosin than adjacent single red cells. Fibrin is not demonstrable in all the sections of each occluded vessel, but is intermingled here and there with the other constitutents. In the human spleen, for example, and in the monkey spleen, small sinuses occur crowded to distension with polymorphonuclear leukocytes, and these obstructed vessels form the centers for minute necroses scattered throughout the spleen so abundantly that in each field of lenses of an amplification of 100 diameters or thereabouts, at least one such lesion is present. The necroses referred to of the ears and skin of the scrotum in guinea-pigs are due apparently to anaemia from the plugging of small blood vessels. In serial sections of ears, the seat of such necrosis, and made from base to the peripheries, the entire gamut of early and late changes which terminate as necrosis are present as well as concomitant results of the altered circulation—edema, hemorrhage, and depositions of blood pigment. In the propagation of the disease the blood serum of an infected animal was sometimes injected into the fresh animal, but the lesions described have nothing to do with the use of alien or homologous serum in the manner indicated, for they are present in the human tissues and organs as well as in those of the animals infected experimentally by tick bites. A possible exception is the presence of rather compact masses of polymorphonuclear leukocytes in the perivascular sheaths of lymphoid tissue in the spleens of monkeys, for in this animal the disease was brought about by the inoculation of blood from an infected guinea-pig or monkey; the disease was not produced by tick bites in any of the monkeys.

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[1] In the spotted fever of Idaho gangrene occurs rather frequently in the human fauces, tonsils, and palate, also in the skin of the penis and scrotum; such changes have not been met with in Montana.

The excess of leukocytes in the vessels, which is such a conspicuous feature in different organs, is in marked contrast to the estimation of the leukocytes made during life; in the sections they seem too numerous to be consistent with estimates of 10 to 14 thousand per cubic millimeter.[1] But we are acquainted with a similar condition in typhoid fever and in acute interstitial nephritis[2] —that is, an apparent disparity between the leukocyte content of the blood during life and the great number in the vessels of certain localities or organs. It would seem, therefore, as though the action of the toxin of this disease was manifest in certain places, and at such points, even though the vessel occlusions were not present, there was likely to be an excess of leukocytes in the blood, mainly of the mononuclear type.

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[1] John A. Anderson (*Hygienic Laboratory Bulletin No. 14*, 1903, p. 22) noted an increase in the large mononuclears in the blood of two patients as the most interesting change from the normal.

[2] Mallory, "The Histology of Typhoid Fever," *Jour. Exp. Med.*, 1898, 3, p. 661; Councilman, "Acute Interstitial Nephritis," *ibid.*, p. 393; Le Count and Batty, "Purpura Hemorrhagica with General ized Infection with B. *paratyphosus*," *Jour. Infect. Dis.*, 1907, 4, p. 175.

No extensive search for the bacillus described by Dr. Ricketts[1] was made. In the examination of the focal lesions it was difficult to dismiss the idea that the cause of the disease was in all likelihood within the field of vision. This was naturally more true of the minuter lesions. The minuteness of the bacillus, and the shrinkage which is probably greater in tissues than in cover-glass preparation, as well as its refractory staining peculiarities, are some of the obstacles to such a search.

It is reasonable to believe that the focal lesions are much more widely spread than has been demonstrated. The bone marrow of a few animals was examined without finding any focal lesions; no human marrow was obtained. Similar necessity for further study concerns the central nervous system. In the few instances in which sections were examined of the cord or brain (some of these had to do with human tissues) no local lesions were seen.

In dismissing this phase of the subject it is proper to liken the focal necroses and the preliminary vessel changes to the alterations caused by the so-called "endothelial toxins"; furthermore, to recall that some such toxins, it is believed, are liberated from the bodies of bacteria.

As for the diffuse changes, the cloudy swelling and fatty changes are not marked. In the lymph glands an hyperplasia occurs and in the spleen a similar process is in part responsible for its considerable enlargement. Hemorrhages are not met with in microscopic preparations of the lymph glands as frequently as in the gross examinations. In two instances, both guinea-pigs killed on the sixth and seventh days of the disease respectively, the microscopic preparations of the lymph glands look not very unlike liver at first glance, due to the great amount of cytoplasm visible with low powers of the microscope and its affinity for the cell-body stains. These large cells crowd and distend the sinuses and are markedly phagocytic.

One of the interesting features of the enlargement of the spleen in guinea-pigs is the appearance of large numbers of multinucleated cells and cells with nuclei aggregated into rings, cells corresponding in some respects to the giant cells of bone marrow. So far as indicated by these megacaryocyte-like cells, this assumption by the spleen of the characteristics of bone marrow was met with in only a few of the spleens of guinea-pigs and then early in the disease. The guinea-pig spleen normally contains such cells in small numbers, but the number present in the spleens of some of the animals is very great. In the human spleens, too, large multinucleated cells possessing some points of resemblance to megacaryocytes are occasionally found, most of them with several small nuclei in the central part of the cell, a few with ring-shaped nuclei. Cells similar to either the megacaryocytes or to multinuclear endothelial cells were absent from the spleens of monkeys. To what extent these large cells in the spleen are to be attributed to a myeloid transformation of the spleen is difficult to state. We are accustomed to attributing similar metaplasias to severe anaemias of some standing.

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[1] *Jour. Am. Med. Assn.*, 1909, 52, p. 379.

In some instances, as for example about the vessels of the guinea-pig's seminal vesicles, in and between tubules of the testes and epididymites of monkeys, some of which had not attained puberty, and in other structures, the accumulations of cells and evidence of their multiplication *in situ* suggest the formation of new depots for the production of leukocytes or other cells which presumably are in some way designed to play some rôle in the defensive processes. These are usually in perivascular situations and so limited to the regions of the lymph channels that it seems unreasonable to ascribe them to the focal processes of blood vessel obstruction and their sequences.

The evidences of obstruction to the outflow of bile are present in the human livers, more marked in some than in others. I have not observed them in the livers of other animals. These changes do not differ in any noteworthy way from those encountered in the livers of persons dying from typhoid fever or lobar pneumonia when an icterus develops during the course of these diseases from retrogressive processes in the liver cells and the resulting interference with the biliary current.

EXPLANATION OF PLATES.

(Figs. 10 [Plate 10], 12 [Plate 11], 15 and 16 [Plate 13] pertain to the more diffuse lesions, the remainder to localized or focal processes.)

PLATE 6.

FIG. 1.—Human Rocky Mountain spotted fever. Minute necrosis in the spleen. ×400 diam.

FIG. 2.—Larger focal necrosis in the human spleen. ×200 diam.

PLATE 7.

FIG. 3.—Human Rocky Mountain spotted fever. In the peripheral capillaries of the liver lobules leukocytes are very numerous, and at various points (*a*) eosin staining rounded masses occur. In some degree they resemble those met with in typhoid fever. ×120 diam.

FIG. 4.—One of the eosin-staining ball-like aggregations, with cell inclusions referred to in Fig. 3. Human. ×400 diam.

PLATE 8.

FIG. 5.—Experimental Rocky Mountain spotted fever. Large subcapsular necrosis in the liver of a guinea-pig. ×200 diam.

FIG. 6.—Experimental Rocky Mountain spotted fever. Small region of necrosis in the liver of a guinea-pig. ×400 diam.

PLATE 9.

FIG. 7.—Thrombosed vein in the skin. Monkey. ×250 diam.

FIG. 8.—Aggregations of leukocytes in the perivascular sheaths in the spleen of a monkey. Experimental Rocky Mountain spotted fever. ×250 diam.

PLATE 10.

FIG. 9.—Illustrating the necrosis of the guinea-pig's ear. ×30 diam.

FIG. 10.—Multinucleated cells in the human spleen. ×700 diam.

PLATE 11.

FIG. 11.—Illustrating the amounts of tissue necrotic in some of the livers of guinea-pigs. ×18 diam.

FIG. 12.—Numerous megacaryocytes in the guinea-pig's spleen. ×80 diam.

PLATE 12.

FIG. 13.—Aggregations of polymorphonuclear leukocytes in perivascular sheaths of lymphoid tissue. Monkey. ×400 diam. Compare with Fig. 8, Plate 9.

FIG. 14.—Collections of fibrin, agglutinated red-blood corpuscles, and leukocytes in the vessels of the renal pyramid. Human. ×45 diam.

PLATE 13.

FIG. 15.—Subintimal proliferation of cells. Human spleen (*a*), mitotic nucleus. ×400 diam.

FIG. 16.—Perivascular accumulations of cells in the wall of the seminal vesicle. Guinea-pig. ×200 diam.

PLATE 6.

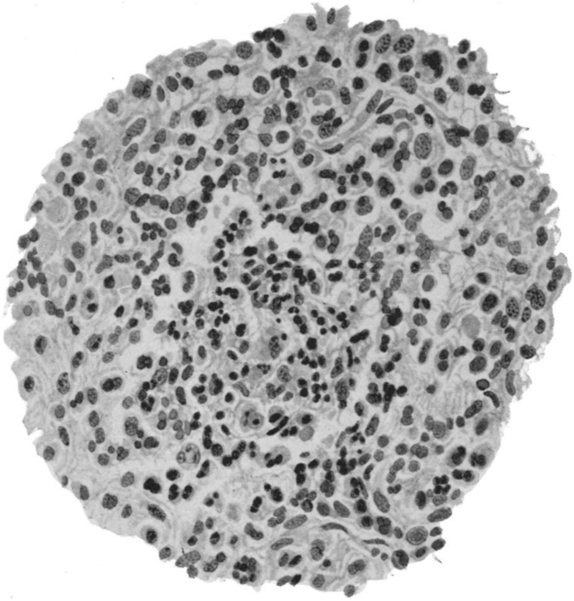


Fig. 1.

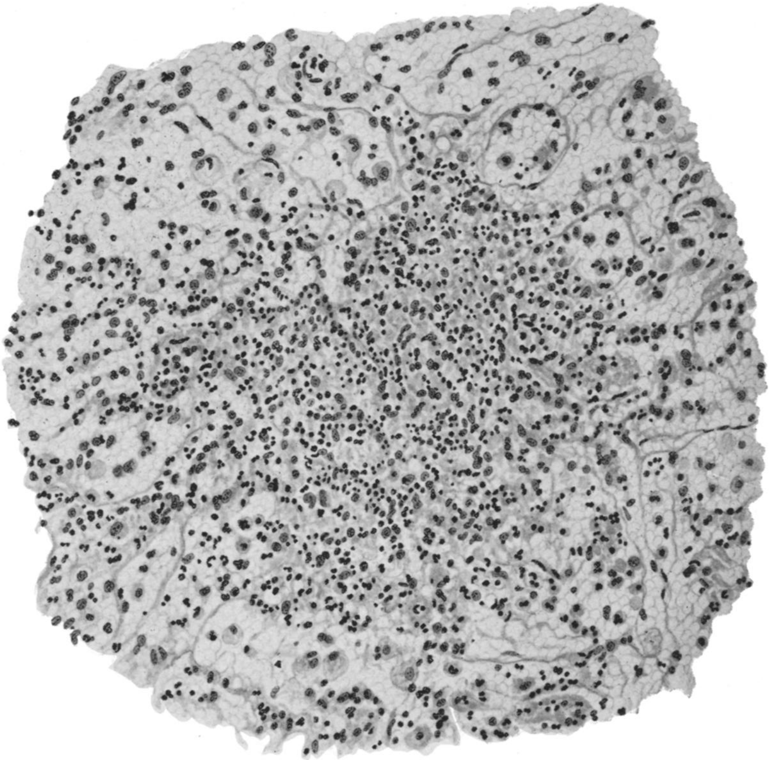


Fig. 2.

PLATE 7.

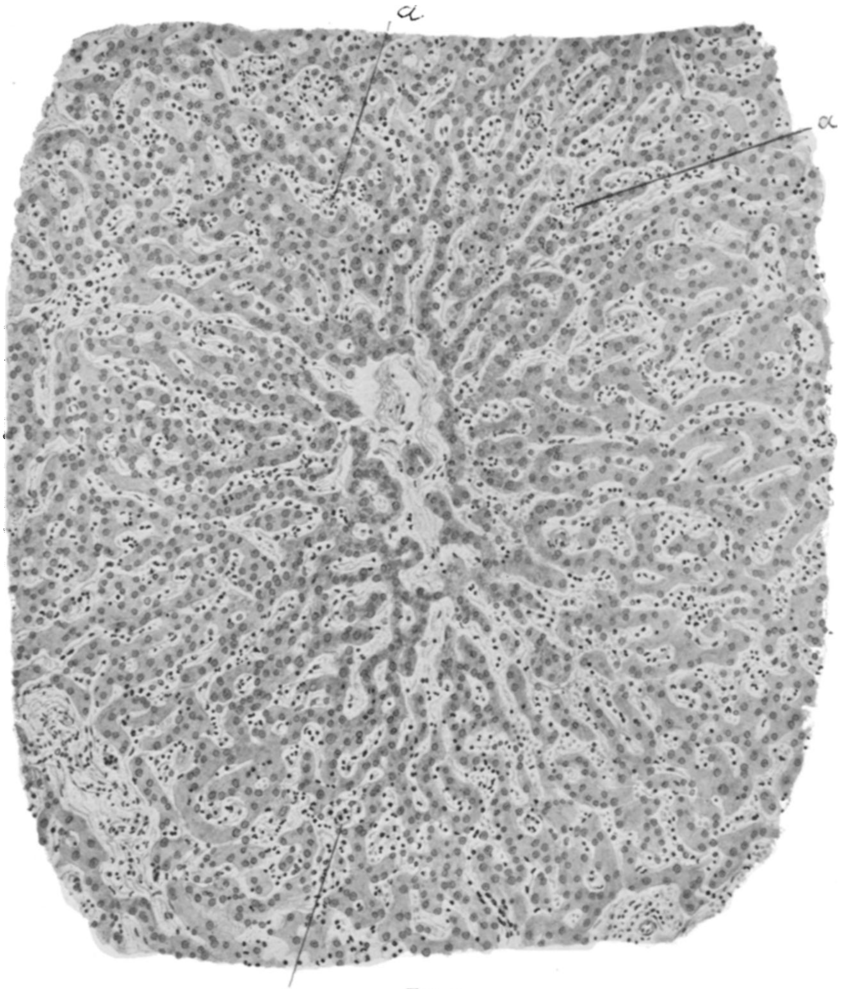


FIG. 3.

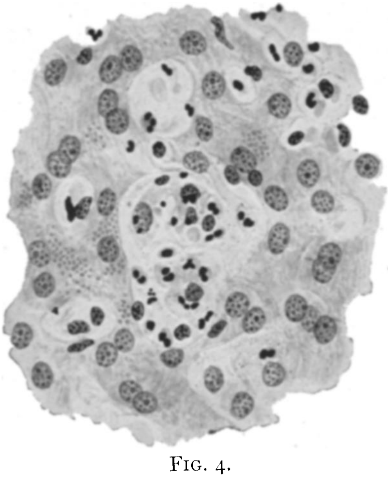
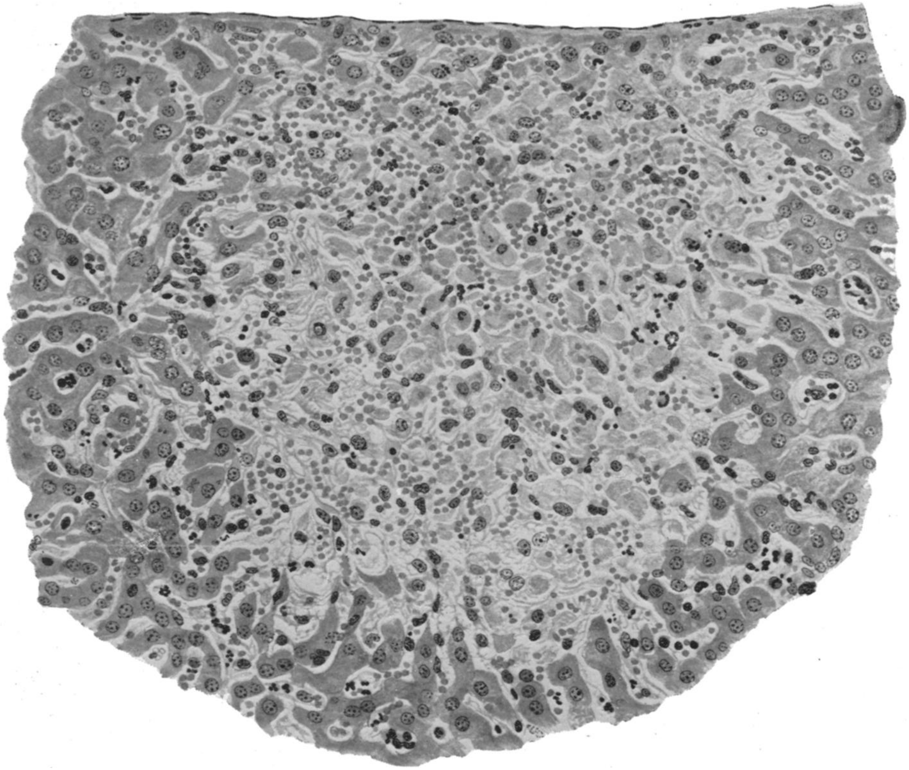


FIG. 4.

PLATE 8.



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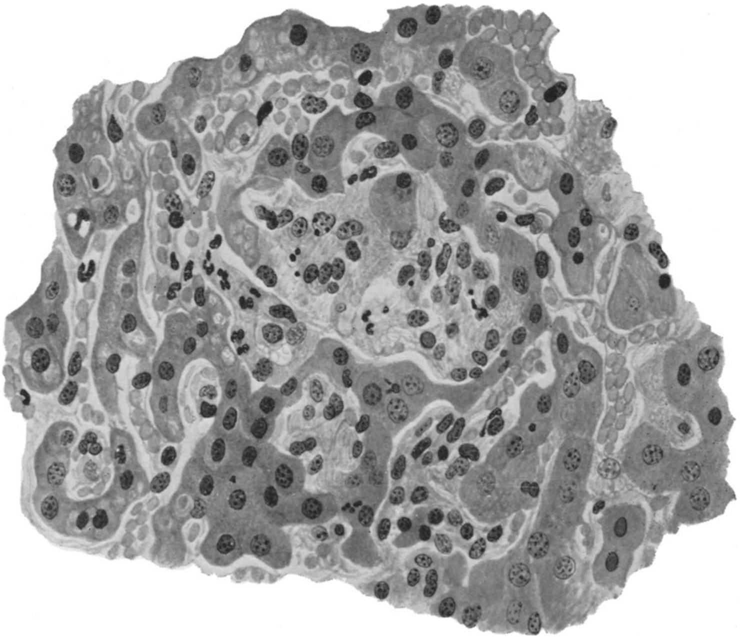
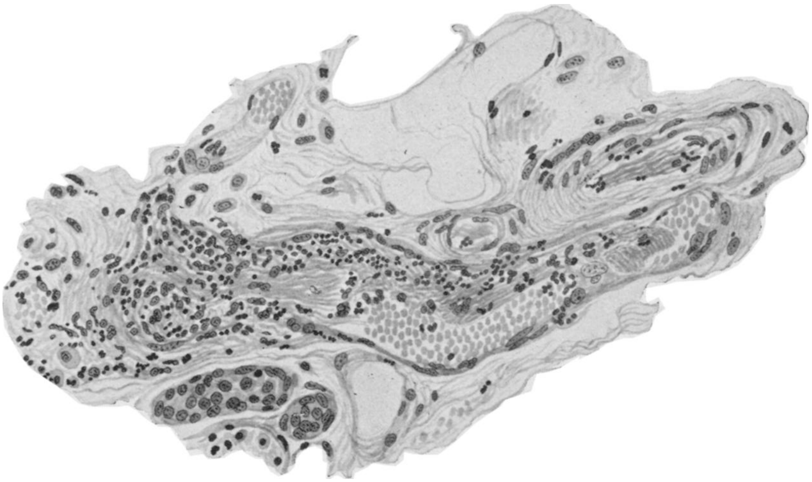


Fig. 6.

PLATE 9.



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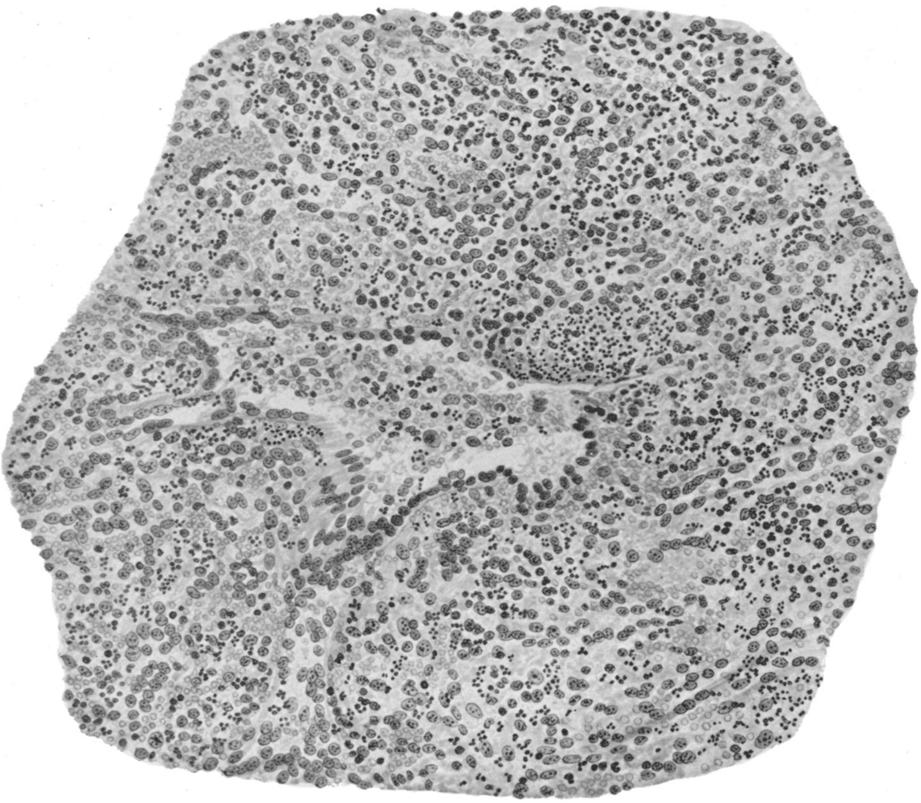
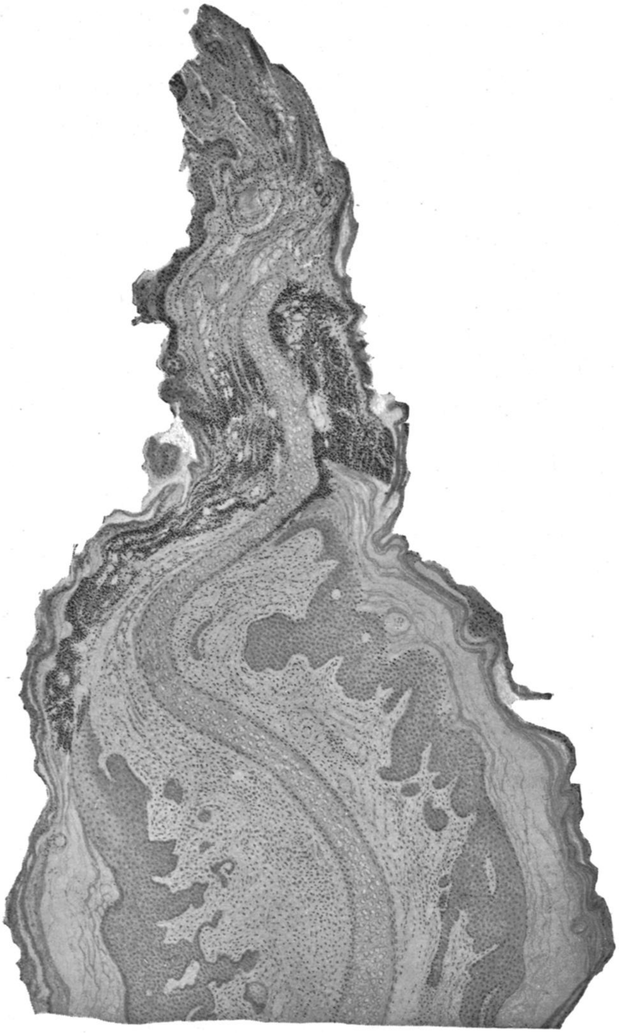


FIG. 8.

PLATE 10.



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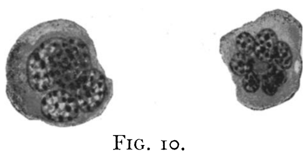

Fig. 10.

PLATE 11.

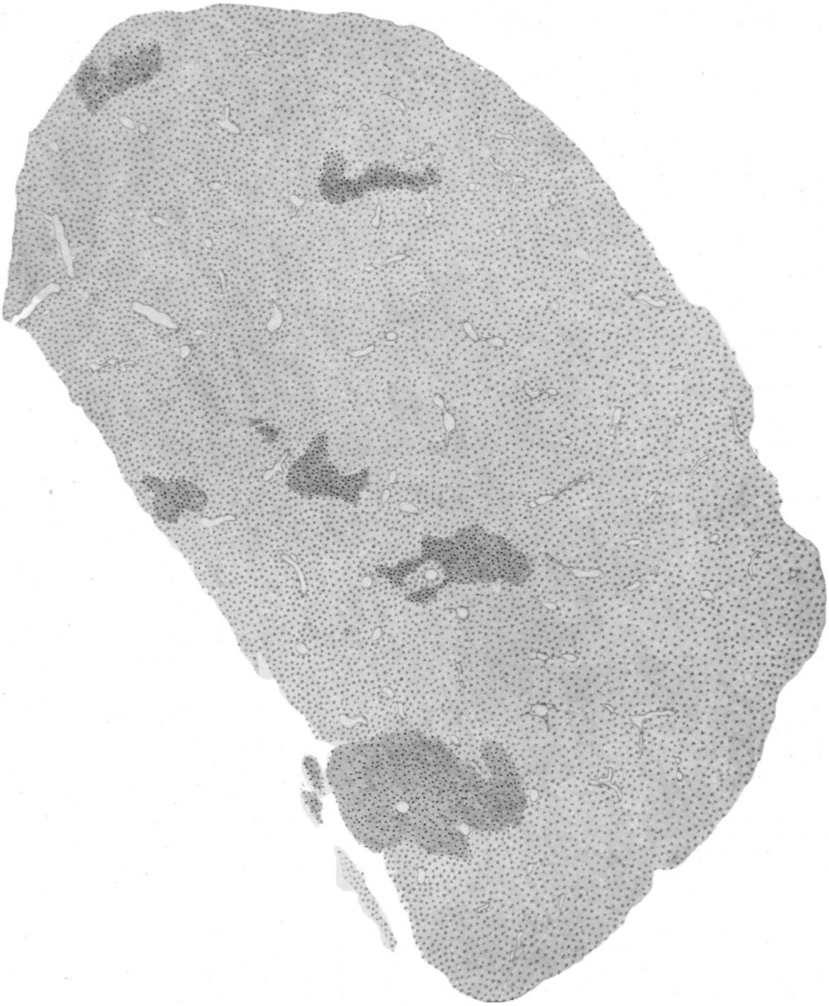

FIG. 11.

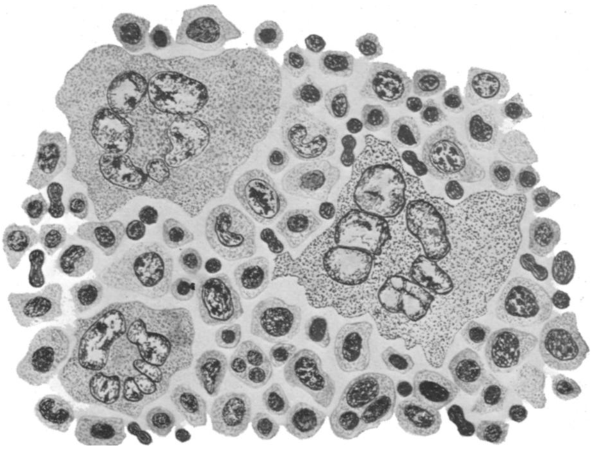

FIG. 12.

PLATE 12.

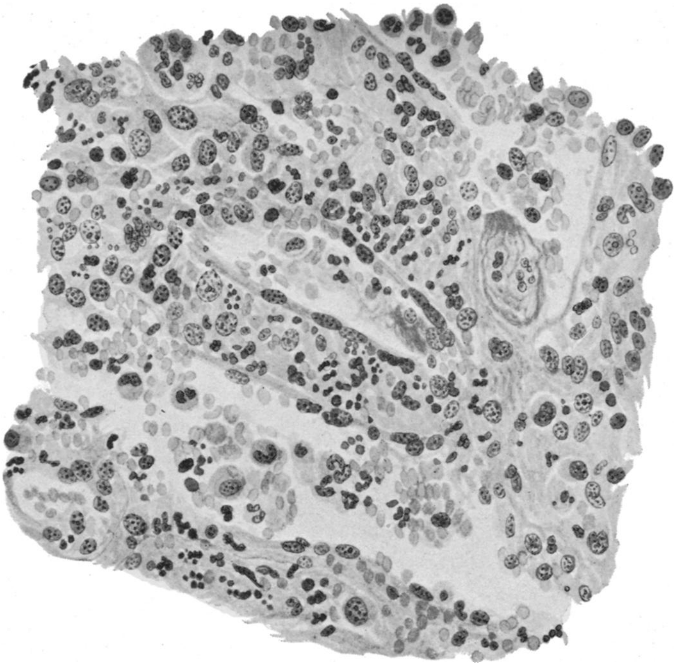

FIG. 13.

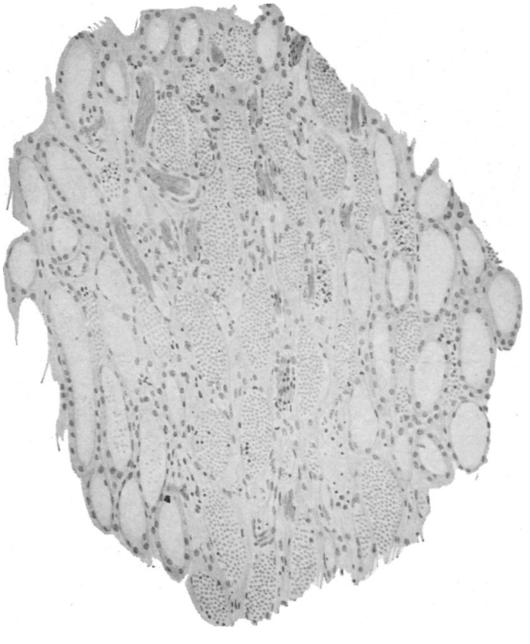

FIG. 14.

PLATE 13.

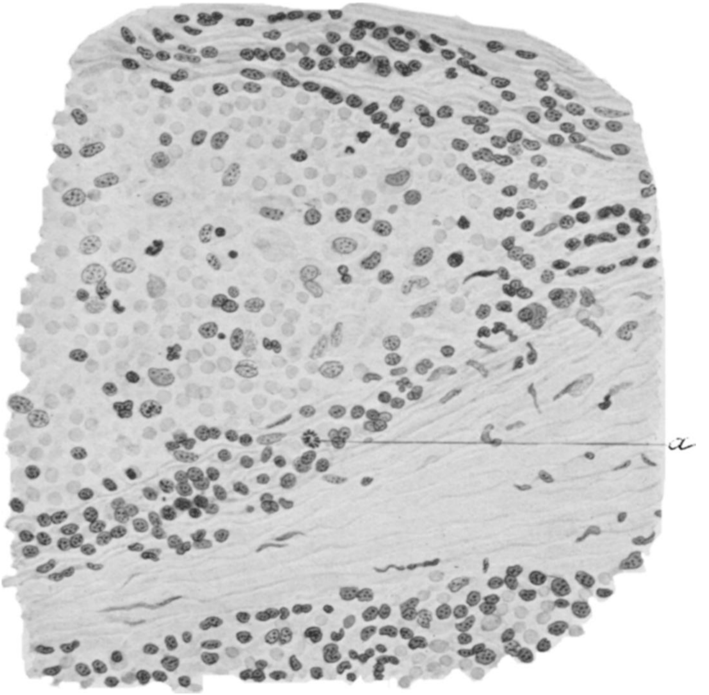

Fig. 15.

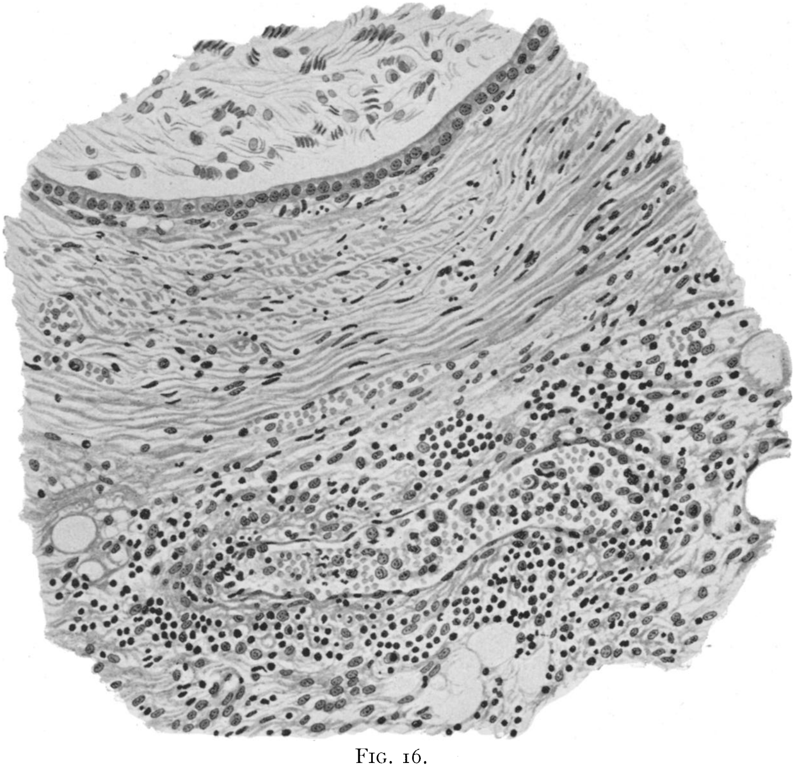

Fig. 16.